

7. PULMONARY ANOMALIES

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PULMONARY HYPOPLASIA

Normal lung development

- 5 stages of embryonic and fetal development:
 - 1) **Embryonal stage**: tracheal/bronchial bud off primitive foregut – see Chapter 3
 - 2) **Pseudoglandular stage**: 8-16 weeks gestation: sequential branching of the bronchial buds (27 generations of branches); end of each terminal bronchiole elicits development of surrounding primitive mesenchyme: epithelial-mesenchymal interaction leads to respiratory units: conducting airway (bronchiole, endoderm) and ‘gland-like’ buds surrounded by capillaries (mesoderm)
 - 3) **Canalicular stage**: 16-25 weeks: further differentiation of terminal airways into conducting and respiratory bronchioles (allows gas exchange by 22-24 weeks)
 - 4) **Terminal sac (saccular) stage**: 25-36 weeks: distal-most bronchioles evolve into sac-like structures: primitive alveoli; interstitial tissue thins out, thereby reducing distance between alveolar space and intravascular space (blood-gas barrier)
 - 5) **Alveolar stage**: 36 weeks to well after birth. Alveolar structures become more complex: ridge- and septum formation leads to more alveoli and greater alveolar surface (increased gas exchange)
- Structural development accompanied by cellular maturation:
 - Epithelium: bronchial cells, alveolar epithelial cells (AEC)
 - AEC further differentiate into type I and type II pneumocytes
 - Type I pneumocytes: line most of the alveole: need to be very thin (minimal cytoplasm allows optimal gas diffusion)
 - Type II pneumocytes: (1-2 cells/alveolus): secretory function (lung fluid in utero; surfactant production): cuboid, organelle-rich cytoplasm, exocytosis
 - Vascular maturation: distal capillaries lose their muscularis, become thin-walled: facilitates gas diffusion and exchange
- Regulation of lung development:
 - “Early” development (up to end of pseudoglandular stage): homeobox genes, FGF-10, branching potential stops at 16 weeks

- “Late gestation” development (from canalicular stage on): maturational stimuli include cellular stretch, epithelial-mesenchymal interaction, paracrine factors
- Factors affecting alveolar stretch may affect further lung growth, maturation, function (and surfactant production)

Impaired lung development

- Final common pathway: inadequate gas exchange at birth
- Spiral: pulmonary hypoplasia → hypoxia, hypercarbia at birth → triggers reflex pulmonary vasoconstriction → pulmonary hypertension → decreased pulmonary blood flow → refractory hypoxemia: regardless of *ventilation*, absence of *perfusion* precludes oxygen uptake: persistent fetal circulation (PFC), ventilation-perfusion mismatch (“R-to-L” shunt)
- May be primary:
 - Error in branching morphogenesis
 - Intrinsic pneumocyte defect
 - Intrinsic vascular anomaly
 - “Idiopathic” pulmonary hypoplasia
 - Pulmonary agenesis
- Secondary pulmonary hypoplasia (PH):
 - Caused by arrested or delayed lung maturation/growth/development
 - Most commonly: impaired effect of alveolar stretch on further development
 - 1) **Absence of fetal breathing:** Rare neurologic conditions – associated with PH.
 - 2) **Impaired chest wall expansion:** fetal breathing present, but impaired by external compression or inadequate chest wall musculature (examples: some forms of muscular dystrophy; prolonged oligohydramnios from any cause: absent kidneys (Potter syndrome), chronic amniotic leak, bladder obstruction)
 - 3) **Space occupying mass in the chest:** Any mass or mass effect may prevent normal expansion of the lung → impaired stretch → pulmonary hypoplasia/immaturity
 - . Congenital lung cyst (sequestration, CCAM, Bronchogenic cyst – see below)
 - . Congenital diaphragmatic hernia (intestines, liver, stomach in chest)

FETAL CONDITIONS RESULTING IN PULMONARY HYPOPLASIA

Congenital diaphragmatic hernia

- Etiology unclear – failure of a portion of the diaphragm to form
 - Most commonly: posterolateral defect (Bochdalek)
 - Left much more common than right

- Anterior defect: Morgagni; commonly small or asymptomatic
- Pathophysiology: herniation of intestines, stomach, liver (degree variable) into the chest cavity → lung compression/impaired lung expansion and stretch → pulmonary hypoplasia
- Rarely symptomatic in fetal life
- Acute hypoxia/hypercarbia at birth (see above)
- Secondary manifestations: if stomach in the chest, may cause upper GI obstruction → impaired swallowing of amniotic fluid → polyhydramnios. Rarely: thoracic compression may cause mediastinal compression, impaired venous return and hydrops
- Grading of severity and prognosis:
 - Poor prognostic factors known – but none predicts outcome with 100% accuracy:
 - Stomach in the chest/polyhydramnios (if isolated, not reliably poor indicator)
 - Liver in the chest
 - Diagnosis <25 weeks (provided, of course, that an U/S was obtained <25 weeks)
 - Lung-Head Ratio (LHR) < 1.0: greatest diameter of contralateral lung/biparietal diameter – good, but not great indicator; fairly reproducible
 - Pulmonary hypoplasia as measured by MRI (see chapter 5B): volumetric determination, water content determination may correlate with lung maturity
 - Associated conditions: chromosomal anomalies (trisomy 18), cardiac anomalies often indicate worse or dismal prognosis
 - Outcome:
 - Improvements in postnatal care and survival: <40% in the 1960, 60-70% today
 - Refined ventilatory strategies: “gentilation” (accept higher pCO₂, avoid barotrauma); nitric oxide; ECMO (extracorporeal membrane oxygenation – pulmonary bypass) for 7-10 days, hoping for catch-up lung maturation
 - Delayed surgical repair: herniated viscera, diaphragmatic defect *not* the primary cause of morbidity/mortality. Better to await pulmonary stabilization, avoid return to persistent fetal circulation caused by stress, hypoxia, acidosis, hypothermia, surgical trauma
 - Significant morbidity in most severe cases: complications of ECMO (intracranial hemorrhage, carotid/jugular vein damage from cannulation), GE reflux, lung damage

Congenital Cystic Adenomatoid Malformation (CCAM)

- Thoracic mass (usually intrapulmonary) containing most lung elements (alveolar, bronchial, parenchymal) in disorganized fashion (hamartoma?); usually mixed cystic/solid.
- If very large: may compress lung (pulmonary hypoplasia), shift mediastinum and cause fetal hydrops and death
- If few large cysts: needle decompression possible; if mostly solid: aspiration not an option
- Difficult to differentiate prenatally from other cystic lung lesions: sequestration, bronchogenic cyst (see below)

- Paradigm shift: 1980s: large lesions believed to cause severe pulmonary hypoplasia, hydrops, death in most/all cases. Now: most (up to 85%?) peak at 20-25 weeks, then regress spontaneously by 26-28 weeks, in time for late lung maturation to occur
- Long-term outcome:
 - if communications with normal airways, may become repeatedly infected
 - reports of malignancy (rhabdomyosarcoma) in CCAM; youngest patient 13 months

Bronchogenic cyst

- Etiology: budding off from primitive tracheobronchial tree formation. The earlier the lesion buds off, the more central it will be located: mediastinal *vs.* peripheral
- Mostly bronchial in origin – contains bronchial lining, cartilage
- Rarely symptomatic before/at birth
- Often incidental finding in childhood or adulthood

Pulmonary sequestration (PS)

- Etiology: like CCAM, contains all elements of bronchial- and lung tissue. Unlike CCAM, sequestration shows organ-like organization of tissues: budding off of peripheral lung unit.
- If develops early: invested with its own pleura, has separate arterial and venous supply (arterial: directly off aorta): “Extralobar” sequestration
- If late development: more likely to be within lung’s own pleura, may have microscopic connections with normal airways (pores of Conn): “Intralobar” sequestration
- Many sequestrations also contain elements of CCAM (hybrid forms – up to 50% of PS)
- Long-term outcome:
 - if communications with normal airways, may become repeatedly infected (Intralobar sequestration)
 - Extralobar sequestration: asymptomatic, good prognosis; but if CCAM elements present: risk of malignancy?

PRENATAL TREATMENT OPTIONS

Overarching goal: allow catch-up lung growth and maturation

Approach: depends on underlying problem

- Intrinsic pulmonary hypoplasia and idiopathic/chromosomal/genetic defects: few, if any options
- Secondary pulmonary hypoplasia: treat the primary problem
 - Bladder outlet obstruction and oligohydramnios: restore urine flow, amniotic fluid – if kidneys functional (see chapter 8)

- Oligohydramnios from chronic amniotic leak: ??seal membrane tear (rarely successful)
 - Idiopathic oligohydramnios: (serial) amnioinfusion tried – mixed results
 - Space-occupying mass: if irreversible (and impending hydrops), decompress chest cavity: needle aspiration if cystic; consider fetal surgery if solid (see chapter 12)
 - Diaphragmatic hernia: decades-old quest, from full surgical repair via open fetal surgery to minimal access fetal tracheal occlusion: lung fluid accumulation causes alveolar stretch and accelerated lung development (see chapter 12)
- Fetal intervention rarely indicated: too aggressive and/or frequent spontaneous resolution without intervention (CCAM, sequestration) and/or improved postnatal treatment (diaphragmatic hernia)

PERINATAL MANAGEMENT OF PULMONARY HYPOPLASIA

Evolving protocols, change in emphasis:

- If impending delivery (premature): use of maternal steroids to accelerate lung maturation
- Minimize ‘oxygenation-at-all-cost,’ provide gentle ventilation (‘gentilation’)
- Minimize barotraumas (iatrogenic lung injury, bronchopulmonary disease (BPD))
- ECMO as bridge to catch-up lung development/maturation
- Diaphragmatic hernia: delayed repair, repair on ECMO
- Use of surfactant (CDH lungs may be surfactant deficient)
- Benefit of multicentric studies, registries, protocols
- If possible, avoid interventions that increase the risk of premature delivery (any fetal intervention): lung disease of prematurity compounds problem of pulmonary hypoplasia
- Novel techniques/interventions: inhaled nitric oxide causes local vasodilatation: i.e., only those alveoli that are ventilated are affected, and only concomitant capillaries dilate: minimizes ventilation/perfusion mismatch and right-to-left shunt

FUTURE DEVELOPMENTS

Further improvements in postnatal treatment

Research:

- Steroids and fetal growth, fetal lung growth, fetal brain development
- Refinements in fetal tracheal occlusion (technique, timing, duration)
- Novel surgical interventions: radiofrequency ablation, thermoablation
- Gene therapy, modulation of apoptosis